

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 309/08, 401/12, C07C 311/44, A61K 31/35</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/40080</b> <b>(43) International Publication Date:</b> 12 August 1999 (12.08.99)
<b>(21) International Application Number:</b> PCT/GB99/00374 <b>(22) International Filing Date:</b> 5 February 1999 (05.02.99)  <b>(30) Priority Data:</b> 9802620.6 6 February 1998 (06.02.98) GB 9819570.4 8 September 1998 (08.09.98) GB  <b>(71) Applicant:</b> DARWIN DISCOVERY LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).  <b>(72) Inventors:</b> MONTANA, John, Gary; Darwin Discovery Lim- ited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). BAXTER, Andrew, Douglas; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). OWEN, David, Alan; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). WATSON, Robert, John; Dar- win Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).  <b>(74) Agent:</b> GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).	<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> HYDROXAMIC AND CARBOXYLIC ACID DERIVATIVES  <b>(57) Abstract</b>  Use of a compound for the manufacture of a medicament for the treatment or prevention of a condition associated with matrix metalloproteinases or that is mediated by TNF $\alpha$ or enzymes involved in the shedding of L-selectin, CD23, the TNF receptors, IL-1 receptors or IL-6 receptors, wherein the compound is of the formula (I): $B-X-(CH_2)_n-CR^2R^3-CR^4R^5-COY$ .		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## HYDROXAMIC AND CARBOXYLIC ACID DERIVATIVES

### Field of the Invention

This invention relates to hydroxamic and carboxylic acid derivatives, and to their use in medicine.

### 5 Background to the Invention

Metalloproteinases, including matrix metalloproteinase (MMP), (human fibroblast collagenase, gelatinase and TNF convertase (TACE), and their modes of action, and also inhibitors thereof and their clinical effects, are described in WO-A-9611209, WO-A-9712902 and WO-A-9719075, the contents of which are incorporated herein by reference.

10 MMP inhibitors may also be useful in the inhibition of other mammalian metalloproteinases such as the adamalysin family (or ADAMs) whose members include TNF convertase (TACE) and ADAM-10, which can cause the release of TNF $\alpha$  from cells, and others, which have been demonstrated to be expressed by human articular cartilage cells and also involved in the destruction of myelin basic protein, a phenomenon associated with multiple

15 sclerosis.

Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown, such as collagenase, stromelysin and gelatinase, have been shown to inhibit the release of TNF both *in vitro* and *in vivo*. See Gearing *et al* (1994), Nature 370:555-557; McGeehan *et al* (1994), Nature 370:558-561; GB-A-2268934; and WO-A-9320047. All of these reported inhibitors contain a hydroxamic acid

20 zinc-binding group, as do the imidazole-substituted compounds disclosed in WO-A-9523790. Other compounds that inhibit MMP and/or TNF are described in WO-A-9513289, WO-A-9611209, WO-A-96035687, WO-A-96035711, WO-A-96035712 and WO-A-96035714.

25 WO-A-9834915 (which may be prior art under Article 54(3) EPC) discloses compounds of formula I (below) wherein B is heterocycloalkyl (optionally substituted by R<sup>6</sup> or R<sup>7</sup>) bonded through carbon to X.

WO-A-9839315 (which may be prior art under Article 54(3) EPC) discloses compounds of formula I (below) wherein R<sup>4</sup> is H and R<sup>5</sup> is unsubstituted C<sub>1-6</sub> alkyl, and

30 B is C<sub>1-8</sub> alkyl optionally substituted by OR<sup>7</sup>.

Summary of the Invention

The invention encompasses novel compounds of formula (I), many of which are novel, which are useful inhibitors of matrix metalloproteinases and/or TNF $\alpha$ -mediated diseases, including degenerative diseases and certain cancers.

- 5 Compounds according to the invention are of the general type represented by formula (I):



wherein

$n = 0-1$ ;

- 10 X is  $\text{S(O)}_{0-2}$ ;

Y is  $\text{OR}^1$  or  $\text{NHOH}$ ;

$\text{R}^2$  and  $\text{R}^4$  are independently H or a group (optionally substituted with  $\text{R}^{10}$ ) selected from  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl, aryl,  $\text{C}_{1-6}$  alkyl-aryl, heteroaryl,  $\text{C}_{1-6}$  alkyl-heteroaryl, heterocycloalkyl,  $\text{C}_{1-6}$  alkyl-heterocycloalkyl, cycloalkyl and  $\text{C}_{1-6}$  alkyl-cycloalkyl; and

- 15  $\text{R}^1$ ,  $\text{R}^3$  and  $\text{R}^5$  are independently H or  $\text{C}_{1-6}$  alkyl;

provided that not more than two of  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are H; or

any of  $\text{CR}^2\text{R}^3$ ,  $\text{CR}^4\text{R}^5$  and  $\text{CR}^2\text{-CR}^4$  is a cycloalkyl or heterocycloalkyl ring optionally substituted with  $\text{R}^{10}$  or a group (optionally substituted with  $\text{R}^{10}$ ) selected from  $\text{C}_{1-6}$  alkyl, aryl,  $\text{C}_{1-6}$  alkyl-aryl, heteroaryl and  $\text{C}_{1-6}$  alkyl-heteroaryl;

- 20 B is heterocycloalkyl (optionally substituted by  $\text{R}^6$  or  $\text{R}^7$ ) bonded through carbon to X, or  $\text{C}_{1-6}$  alkyl-heterocycloalkyl (optionally substituted with  $\text{R}^6$  or  $\text{R}^7$ ), or a group (substituted with  $\text{R}^6$ ) selected from  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl and  $\text{C}_{2-6}$  alkynyl;

$\text{R}^6$  is  $\text{N(R}^7\text{)}_2$ ,  $\text{OR}^7$ ,  $\text{COR}^7$ ,  $\text{C(=NOR}^9\text{)R}^7$ ,  $\text{NR}^7\text{R}^8$ ,  $\text{S(O)}_{0-2}\text{R}^9$  or  $\text{SO}_2\text{N(R}^7\text{)}_2$ ;

- 25  $\text{R}^7$  is H or a group selected from  $\text{C}_{1-6}$  alkyl, aryl,  $\text{C}_{1-6}$  alkyl-aryl, heteroaryl,  $\text{C}_{1-6}$  alkyl-heteroaryl, cycloalkyl,  $\text{C}_{1-6}$  alkyl-cycloalkyl, heterocycloalkyl and  $\text{C}_{1-6}$  alkyl-heterocycloalkyl, wherein said group is optionally substituted with  $\text{R}^9$ ,  $\text{COR}^9$ ,  $\text{SO}_{0-2}\text{R}^9$ ,  $\text{CO}_2\text{R}^9$ ,  $\text{OR}^9$ ,  $\text{CONR}^1\text{R}^9$ ,  $\text{NR}^1\text{R}^9$ , halogen, CN,  $\text{SO}_2\text{NR}^1\text{R}^9$  or  $\text{NO}_2$ , and for each case of  $\text{N(R}^7\text{)}_2$  the  $\text{R}^7$  groups are the same or different or  $\text{N(R}^7\text{)}_2$  is heterocycloalkyl optionally substituted with  $\text{R}^9$ ,  $\text{COR}^9$ ,  $\text{SO}_{0-2}\text{R}^9$ ,  $\text{CO}_2\text{R}^9$ ,  $\text{OR}^9$ ,  $\text{CONR}^1\text{R}^9$ ,  $\text{NR}^1\text{R}^9$ , halogen, CN,  
30  $\text{SO}_2\text{NR}^1\text{R}^9$  or  $\text{NO}_2$ ;

$\text{R}^8$  is  $\text{COR}^7$ ,  $\text{CON(R}^7\text{)}_2$ ,  $\text{CO}_2\text{R}^9$  or  $\text{SO}_2\text{R}^9$ ;

$\text{R}^9$  is  $\text{C}_{1-6}$  alkyl, aryl,  $\text{C}_{1-6}$  alkyl-aryl, heteroaryl or  $\text{C}_{1-6}$  alkyl-heteroaryl; and

$R^{10}$  is  $OR^7$ ,  $COR^7$ ,  $CO_2R^1$ ,  $CON(R^7)_2$ ,  $NR^7R^8$ ,  $S(O)_{0-2}R^9$ ,  $SO_2N(R^7)_2$ , CN, halogen or cycloimidyl (optionally substituted with  $R^1$ );

and the salts, solvates, hydrates, N-oxides, protected amino, protected carboxy and protected hydroxamic acid derivatives thereof.

- 5 Combinations of substituents and/or variables are only permissible if such combinations result in stable compounds.

#### Description of the Invention

Preferred compounds of the invention are those wherein any one or more of the following apply:

- 10 X is  $SO_2$ ,

Y is  $NHOH$ ;

$R^2$  or  $R^4$  are optionally substituted  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl-heteroaryl, or  $C_{1-6}$  alkyl-heterocycloalkyl; or  $R^2$  and  $R^3$ , or  $R^4$  and  $R^5$ , or  $R^2$  and  $R^4$  form the said optionally substituted cycloalkyl or heterocycloalkyl groups;

- 15 B is  $C_{1-8}$  alkyl substituted with  $R^6$ ; and  
 $R^6$  is  $OR^7$ .

The compounds of the Examples are particularly preferred.

- It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres in a compound of formula (I) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

- It will further be appreciated that the compounds according to the invention may contain an oxime. This oxime can give rise to geometrical isomers, and in each case the invention is to be understood to extend to all such isomers and mixtures thereof.

As used in this specification, alone or in combination, the term " $C_{1-6}$  alkyl" refers to straight or branched chain alkyl moiety having from one to six carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like.

- The term " $C_{1-8}$  alkyl" refers to straight or branched chain alkyl moiety having from one to eight carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl, octyl and the like.

The term " $C_{2-6}$  alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2- butenyl, 2- methyl-2-propenyl etc.

5 The term " $C_{2-6}$  alkynyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2- butynyl, 1- methyl-2-butynyl etc.

The term "cycloalkyl" refers to a saturated alicyclic moiety having from three to six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl  
10 and the like.

The term "heterocycloalkyl" refers to a saturated heterocyclic moiety having from two to six carbon atoms and one or more heteroatom from the group N, O, S (or oxidised versions thereof) which may be optionally benzofused at any available position. This includes for example azetidiny, pyrrolidiny, tetrahydrofurany, piperidiny, benzodioxole  
15 and the like.

The term "aryl" refers to an aromatic carbocyclic radical having a single ring or two condensed rings. This term includes, for example phenyl or naphthyl.

The term "heteroaryl" refers to aromatic ring systems of five to ten atoms of which at least one atom is selected from O, N and S, and includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like.  
20

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "benzofused" refers to the addition of a benzene ring sharing a common bond with the defined ring system.

The term "cycloimidyl" refers to a saturated ring of five to ten atoms containing the atom sequence  $-C(=O)NC(=O)-$ . The ring may be optionally benzofused at any available position. Examples include succinimidoyl, phthalimidoyl and hydantoinyl.  
25

The term "optionally substituted" means optionally substituted with one or more of the groups specified, at any available position or positions.

The terms "protected amino", "protected carboxy" and "protected hydroxamic acid" mean amino, carboxy and hydroxamic acid groups which can be protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzyloxycarbonyl, *tert*-butoxycarbonyl, acetyl or like group, or may be in the  
30

form of a phthalimido or like group. A carboxyl group can be protected in the form of a readily-cleavable ester such as the methyl, ethyl, benzyl or *tert*-butyl ester. A hydroxamic acid may be protected as either N or O-substituted derivatives, such as O-benzyl or O-*tert*-butyldimethylsilyl.

5        Salts of compounds of formula (I) include pharmaceutically-acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, p-toluenesulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

10       Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

When the "protected carboxy" group in compounds of the invention is an esterified  
15       carboxyl group, it may be a metabolically-labile ester of formula  $\text{CO}_2\text{R}^{11}$  where  $\text{R}^{11}$  may be an ethyl, benzyl, phenethyl, phenylpropyl,  $\alpha$ - or  $\beta$ -naphthyl, 2,4-dimethylphenyl, 4-*tert*-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypentyl, 2,4,6-trimethylbenzyloxymethyl or pivaloylmethyl group.

Compounds of the general formula (I) may be prepared by any suitable method  
20       known in the art and/or by the following processes.

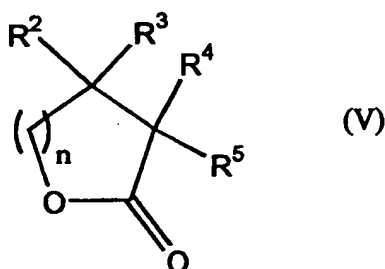
It will be appreciated that, where a particular stereoisomer of formula (I) is required, the synthetic processes described herein may be used with the appropriate homochiral starting material and/or isomers may be resolved from mixtures using conventional separation techniques (e.g. HPLC).

25       The compounds according to the invention may be prepared by the following process. In the description and formulae below the groups  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^8$ ,  $\text{R}^9$ ,  $\text{R}^{10}$ ,  $\text{R}^{11}$ , B, X and Y are as defined above, except where otherwise indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to  
30       be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups

for such functionality will be apparent to those skilled in the art. For specific details see Greene *et al*, "Protective Groups in Organic Synthesis", Wiley Interscience.

A process for preparing compounds of general formula (I) comprises reacting a compound of formula B-SH (II) with (a) an alkylating agent of formula  $Z-(CH_2)_n-CR^2R^3-$   
 5  $CR^4R^5-COY$  (III) (wherein Z represents a suitable leaving group e.g. a halogen such as bromine, or an alkylsulphonate ester such as methanesulphonate), or (b) (when  $n = 0$  and  $R^5 = H$ ) an acrylate of formula  $CR^2R^3=CR^4-COY$  (IV) or (c) a lactone of the formula (V)

10



An alternative process for preparing compounds of formula (I) involves reacting  
 15 a compound of formula B-Z (VI) with a compound of formula  $Q-S-(CH_2)_nCR^2R^3CR^4R^5COY$  (VII), where Z is defined above and Q is a suitable labile group, such as acetyl, in the presence of a strong base such as hexamethyldisilazide in an inert solvent such as tetrahydrofuran. Compounds of formula (VII) may be prepared by reaction of a compound of formula QSH (VIII) with a compound (III), (IV) or (V) as  
 20 defined above, optionally in the presence of an organic or inorganic base.

Alkylating agents of formula (III) can be obtained in chiral or racemic form. Many of these derivatives can be readily obtained from commercially available starting materials using methods known to those skilled in the art (e.g. see WO-A-9005719).

Acrylates of formula (IV) may be prepared by the condensation of a carbonyl  
 25 compound of the form  $R^4CH_2COY$  (IX) with ketones or aldehydes of formula  $R^2COR^3$  (X). This reaction may be performed under a variety of conditions known to those skilled in the art, for example under the action of a strong base such as lithium diisopropylamide in an inert solvent such as tetrahydrofuran, to give an intermediate alcohol of the form  $R^2C(OH)R^3CHR^4COY$  (XI). These alcohols (XI) may or may not be isolated: dehydration  
 30 may occur *in situ* or be performed separately under appropriate conditions such as aqueous acid to give the desired acrylate (IV).



Lactones of formula (V) may be prepared by chemistry known to those skilled in the art. For example see EP-A-0780386.

Many compounds of formula (II) are available commercially, or may be prepared from compounds of the form B-Z (VI) by standard methods (for example, see WO-A-9611209).

Many compounds of formula (VIII), (VI), (IX) and (X) are available commercially, or may be prepared from compounds available commercially by standard methods. Other substituents described by  $R^2$ ,  $R^4$ , or  $R^6$  or can be introduced by standard chemical transformations known to those skilled in the art.

Compounds of formula (I) may also be prepared by interconversion of other compounds of formula (I). Thus, for example, a compound of formula (I) wherein  $R^2$  is a  $C_{1-6}$  alkyl group may be prepared by hydrogenation (using palladium on carbon in suitable solvent, such as an alcohol, e.g. ethanol) of a compound of formula (I) wherein  $R^2$  is a  $C_{2-6}$  alkenyl group. Further, a compound of formula (I) wherein X is  $S(O)_{1-2}$  may be prepared by oxidation of a compound of formula (I) wherein X is S.

Carboxylic acids of general formula (I) ( $Y=OH$ ) may be converted to other compounds of formula (I) such as esters ( $Y=OR^1$ ) or hydroxamic acids ( $Y=NHOH$ ) using methods known to those skilled in the art.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

The compounds according to the invention exhibit *in vitro* inhibiting activities with respect to the stromelysins, collagenases and gelatinases. Compounds according to the invention may also exhibit *in vitro* inhibition of membrane shedding events known to be mediated by metalloproteinases, for example,  $\alpha$ -APP, ACE, TGF- $\alpha$ , TNF- $\alpha$ , Fas ligand, TNFR-I, TNFR-II, CD30, IL-6R, CD43, CD44, CD16-I, CD16-II, Folate receptor, CD23, or IL-1RII.

The activity and selectivity of the compounds may be determined by use of the appropriate enzyme inhibition test, for example as described in Examples A-M of WO-A-

9805635, by the assay for the inhibition of CD23 shedding described in PCT/GB98/03395, or by the following assay of TNF RI shedding.

The potency of the compounds of general formula (I) to act as inhibitors of the production of TNF RI is determined using the following procedure. A 100 $\mu$ M solution of the inhibitor being tested or dilutions thereof is incubated at 37° C in an atmosphere of 5% CO<sub>2</sub> with peripheral blood mononuclear cells (PBMC). PBMC are isolated from buffy coats by standard procedures using Ficoll. A 100 $\mu$ M solution of the inhibitor being tested or dilutions thereof is incubated for 22 hours at 37° C in an atmosphere of 5% CO<sub>2</sub> with 1 x 10<sup>6</sup>/ml PBMC stimulated with LPS. The cells are centrifuged down and the supernatant is assayed for TNF RI using a commercially available ELISA kit (R & D Systems). The activity in the presence of 0.1 mM inhibitor or dilutions thereof is compared to activity in a control devoid of inhibitor and results reported as that inhibitor concentration effecting 50% inhibition of the production of TNF RI.

This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from disorders or diseases which can be attributed to stromelysin as previously described, and more specifically, a method of treatment involving the administration of the matrix metalloproteinase inhibitors of formula (I) as the active constituents.

Accordingly, the compounds of formula (I) can be used among other things in the treatment of osteoarthritis and rheumatoid arthritis, and in diseases and indications resulting from the over-expression of these matrix metalloproteinases such as found in certain metastatic tumour cell lines.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine since they are active as inhibitors of TNF and MMPs. Accordingly in another aspect, this invention concerns:

- a method of management (by which is meant treatment or prophylaxis) of disease or conditions mediated by TNF and/or MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective, amount of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof; and
- a compound of formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs; and

the use of a compound of formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs.

The disease or conditions referred to above include inflammatory diseases, autoimmune diseases, cancer, cardiovascular diseases, diseases involving tissue breakdown such as rheumatoid arthritis, osteoarthritis, osteoporosis, neurodegeneration, Alzheimer's disease, stroke, vasculitis, Crohn's disease, ulcerative colitis, multiple sclerosis, periodontitis, gingivitis and those involving tissue breakdown such as bone resorption, haemorrhage, coagulation, acute phase response, cachexia and anorexia, acute infections, HIV infections, fever, shock states, graft versus host reactions, dermatological conditions, surgical wound healing, psoriasis, atopic dermatitis, epidermolysis bullosa, tumour growth, angiogenesis and invasion by secondary metastases, ophthalmological disease, retinopathy, corneal ulceration, reperfusion injury, migraine, meningitis, asthma, rhinitis, allergic conjunctivitis, eczema, anaphylaxis, restenosis, congestive heart failure, endometriosis, atherosclerosis, endosclerosis and aspirin-independent anti-thrombosis.

Compounds of formula (I) may also be useful in the treatment of pelvic inflammatory disease (PID), age-related macular degeneration and cancer-induced bone resorption. Further, they can be used in the treatment of lung diseases, e.g. selected from cystic fibrosis, adult respiratory distress syndrome (ARDS), emphysema, bronchitis obliterans-organising pneumonia (BOOP), idiopathic pulmonary fibrosis (PIF), diffuse alveolar damage, pulmonary Langerhan's cell granulomatosis, pulmonary lymphangiioleiomyomatosis (LAM) and chronic obstructive pulmonary disease (COPD).

For the treatment of rheumatoid arthritis, osteoarthritis, and in diseases and indications resulting from the over-expression of matrix metalloendoproteinases such as found in certain metastatic tumour cell lines or other diseases mediated by the matrix metalloendoproteinases or increased TNF production, the compounds of formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the treatment of humans.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the US Patents 4,256,108; 4,166,452; and 4,265,874, to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules where in the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of

ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or  
5 more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for  
10 example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous  
15 suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-  
20 water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate  
25 and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent,  
30 a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting

agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc containing the compounds of Formula (I) are employed. For the purposes of this specification, topical application includes mouth washes and gargles.

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above- indicated conditions (about 2.5 mg to about 7 g per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 g per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95% of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following Examples illustrate the invention. The following abbreviation is used:

RT = Room Temperature DMF = Dimethylformamide THF = Tetrahydrofuran

**Intermediate 1      2,7-Dioxaspiro[3.5]nonan-1-one**

5      Was prepared according to the procedure outlined in EP-A-0780386, as a colourless oil (5.2 g).

**Intermediate 2      1-Bromo-3-(4-chlorophenoxy)propane**

Sodium hydride (3.3 g, 60% dispersion in oil) was added to a solution of 4-chlorophenol (9.0 g) in DMF (30 ml) at 0°C and the mixture was stirred for 30 min, then  
10      1,3-dibromopropane (22.5 g, 1.5 eq) was added. The mixture was stirred at room temperature for 18 h, then added to water (300 ml) and extracted with ether. The solvent was washed with 5% NaOH and brine, dried over MgSO<sub>4</sub> and evaporated and the residue purified on silica gel, eluting with 1:1 ether/hexane, to give the title compound (13.5 g) as a colourless oil.

15      TLC R<sub>f</sub> 0.73 (ether).

**Intermediate 3      1-Acetylsulfanyl-3-(4-chlorophenoxy)propane**

A solution of Intermediate 2 (6.0 g) in DMF (50 ml) was treated with potassium thioacetate (5.7 g) at room temperature for 3 h, then the brown solution was added to 5% sodium bicarbonate solution and extracted with ether (3 x 200 ml). The solvent was  
20      washed with water (200 ml) and brine, dried over MgSO<sub>4</sub> and evaporated to give the title compound (5.50 g) as a beige solid.

TLC R<sub>f</sub> 0.54 (ether).

**Intermediate 4      Methyl 4-Iodomethyl-tetrahydropyran-4-carboxylate**

To a stirred solution of methyl tetrahydropyran-4-carboxylate (3.00 g) in  
25      anhydrous THF (50 ml) under nitrogen at 0°C was added a solution of lithium diisopropylamide (2.0 M, 10.9 ml). After 30 minutes, diiodomethane (8.36 g) was added and the mixture was allowed to warm up to RT and then stirred for 1 h. The mixture was poured onto water (50 ml) and extracted with ether (3 x 40 ml). The combined ether layers were washed with water (2 x 20 ml), aqueous hydrochloric acid (2 M, 20 ml), water  
30      (20 ml) and brine (20 ml), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified on silica gel, eluting with 3:1 hexane/ether, to give the title compound (3.11 g) as a colourless oil.

TLC  $R_f$  0.26 (3:1 hexane/ether)

**Intermediate 5**      **Methyl 4-Acetylsulfanylmethyl-tetrahydropyran-4-carboxylate**

A solution of Intermediate 4 (3.05 g) in DMF (20 ml) was treated with potassium thioacetate (1.47 g) at room temperature for 18 h, then the brown solution was added to  
5 5% sodium bicarbonate solution and extracted with ether (3 x 200 ml). The solvent was washed with water (200 ml) and brine, dried over  $MgSO_4$  and evaporated to give the title compound (2.42 g) as a white solid.

TLC  $R_f$  0.44 (1:1 hexane/ether).

**Example 1**      **4-((3-(4-Chlorophenoxy)propylsulfanyl)methyl)-tetrahydropyran-4-carboxylic Acid**

A solution of Intermediate 3 (0.80 g) in methanol was treated with a solution of sodium hexamethyldisilazide (1 M in THF, 3.3 ml) at 0°C and the resulting mixture was stirred for 2 h, then a solution of Intermediate 1 (460 mg) in methanol was added. The mixture was stirred for 18 h, then evaporated and the residue dissolved in water and  
15 washed with diethyl ether. The aqueous phase was acidified with citric acid and extracted with dichloromethane; the organic layer was then washed with brine, dried over  $MgSO_4$  and evaporated to give the title compound (0.12 g) as a colourless oil.

TLC  $R_f$  0.54 (ether)

**Example 2**      **Methyl 4-(3-Hydroxypropylsulfanylmethyl)tetrahydropyran-4-carboxylate**

To a stirred solution of Intermediate 5 (2.50 g) in methanol (100 ml) under nitrogen at 0°C was added a solution of sodium hexamethyldisilazide (1M in THF, 11.3 ml) and the resulting mixture was stirred for 10 mins, then a solution of 3-bromopropanol (1.5 g) was added. The mixture was stirred for 6 h, then evaporated and the residue  
25 treated with water (100 ml) and extracted with dichloromethane (4 x 50 ml). The combined dichloromethane extracts were washed with water (2 x 50 ml), brine (50 ml), dried over  $MgSO_4$  and evaporated. The residue was purified on silica gel eluting with 2:1 ethyl acetate/hexane, to give the title compound (2.41 g) as a colourless oil.

TLC  $R_f$  0.26 (2:1 ethyl acetate/hexane).



**Example 3**                      **Methyl 4-((3-(4-Methoxyphenoxy)propylsulfanyl)methyl)-tetrahydropyran-4-carboxylate**

To a stirred solution of Example 2 (500 mg) and triphenylphosphine (528 mg) in dry THF (25 ml) at 0°C under nitrogen, was added diethylazodicarboxylate (351 mg).

- 5 After 5 min a solution of 4-methoxyphenol (250 mg) in THF was added. The mixture was stirred for 2 h with the temperature rising to RT, then poured into ether (100 ml) and washed with water (2 x 25 ml), sodium hydroxide solution (1M; 25 ml), brine (25ml) and dried over MgSO<sub>4</sub>. Evaporation and purification on silica gel eluting with 2:1 hexane/ethyl acetate, gave the title compound (415 mg) as a colourless oil.
- 10 TLC R<sub>f</sub> 0.25 (2:1 hexane/ethyl acetate).

Similarly prepared were:

**Example 4**                      **Methyl 4-((3-(4-Phenylphenoxy)propylsulfanyl)methyl)-tetrahydropyran-4-carboxylate**

From Example 2 (500 mg) and 4-phenylphenol (343 mg) as a white solid (298 mg).

- 15 TLC R<sub>f</sub> 0.45 (2:1 hexane/ethyl acetate).

**Example 5**                      **Methyl 4-((3-(3-Pyridyloxy)propylsulfanyl)methyl)-tetrahydropyran-4-carboxylate**

From Example 2 (500 mg) and 3-hydroxypyridine (191 mg) as a colourless oil (360 mg).

- 20 TLC R<sub>f</sub> 0.19 (2:1 ethyl acetate/hexane).

**Example 6**                      **Methyl 4-((3-(4-Methoxyphenoxy)propylsulfonyl)methyl)-tetrahydropyran-4-carboxylate**

To a stirred solution of Example 3 (400 mg) in methanol (10 ml) at RT was added a solution of Oxone (1.04 g) in water (20 ml). Stirring was continued for 18 h before

- 25 diluting with water (50 ml) and extracting with dichloromethane (4 x 25 ml). The combined organic layers were washed with water (25 ml), brine (25 ml), dried over MgSO<sub>4</sub> and evaporated to give the title compound (385 mg) as a colourless oil.
- TLC R<sub>f</sub> 0.33 (2:1 ethyl acetate/hexane).

Similarly prepared were:

30 **Example 7**                      **Methyl 4-((3-(4-Phenylphenoxy)propylsulfonyl)methyl)-tetrahydropyran-4-carboxylate**

From Example 4 (290 mg) as a white solid (303 mg).

TLC R<sub>f</sub> 0.33 (2:1 ethyl acetate/hexane).

**Example 8**                      **Methyl 4-((3-(3-Pyridyloxy)propylsulfonyl)methyl)-  
tetrahydropyran-4-carboxylate**

From Example 5 (325 mg) as a colourless oil (350 mg).

5    TLC R<sub>f</sub> 0.15 (ethyl acetate).

**Example 9**                      **4-((3-(4-Chlorophenoxy)propylsulfonyl)methyl)-  
tetrahydropyran-4-carboxylic Acid**

Oxone (0.42 g) was added to a solution of Example 1 (0.12 g) in methanol (10 ml) and water (5 ml) at room temperature and the mixture was stirred for 3 h. The mixture  
10    was then evaporated to half volume, diluted with water (5 ml) and extracted with dichloromethane (2 x 20 ml). The organic layer was then washed with brine, dried over MgSO<sub>4</sub> and evaporated and the residue purified by flash column chromatography on silica gel, eluting with ethyl acetate/acetic acid (99:1) to give the title compound (70 mg) as a white solid.

15    TLC R<sub>f</sub> 0.70

MS 376 (M<sup>+</sup>)

**Example 10**                      **4-((3-(4-Methoxyphenoxy)propylsulfonyl)methyl)-  
tetrahydropyran-4-carboxylic Acid**

To a stirred solution of Example 6 (380 mg) in methanol (30 ml) was added a  
20    solution of lithium hydroxide (206 mg) in water (10 ml). The mixture was refluxed for 1.5 h, cooled to RT and diluted with water (50 ml). The aqueous mixture was washed with ether (2 x 20 ml), acidified (2M HCl, pH1) and extracted with ethyl acetate (5 x 25ml). The combined ethyl acetate fractions were washed with water (2 x 20 ml), brine (20ml), dried over MgSO<sub>4</sub> and evaporated to give the title compound (266 mg) as a white solid.

25    TLC R<sub>f</sub> 0.10 (ethyl acetate)

MS 372 (M<sup>+</sup>)

Similarly prepared were:

**Example 11**                      **4-((3-(4-Phenylphenoxy)propylsulfonyl)methyl)-  
tetrahydropyran-4-carboxylic Acid**

30                      From Example 7 (300 mg) as a white solid (203 mg).

TLC R<sub>f</sub> 0.15 (ethyl acetate)

MS 418 (M<sup>+</sup>)

**Example 12**                    **4-((3-(3-Pyridyloxy)propylsulfonyl)methyl)tetrahydropyran-4-carboxylate**

From Example 8 (325 mg) as a white solid (103 mg).

TLC R<sub>f</sub> 0.10(ethyl acetate)

5 MS 343 (M<sup>+</sup>)

**Example 13**                    **4-((3-(4-Chlorophenoxy)propylsulfonyl)methyl)-tetrahydropyran-4-carboxylic Acid N-Hydroxy Amide**

EDC (40 mg) was added to a solution of Example 9 (75 mg) in dichloromethane (20 ml), followed by *tert*-butyldimethylsilylhydroxylamine (32 mg) and *N,N*-dimethylaminopyridine (2 mg), and the resulting clear solution was stirred at room temperature for 3 h. The mixture was then washed with water, saturated bicarbonate and brine, dried over MgSO<sub>4</sub> and evaporated. The residue was dissolved in a minimum amount of fresh dichloromethane and 1M aqueous hydrochloric acid in ether (2 ml) was added. The solution was stirred for 10 min, then evaporated and the residue purified by chromatography on silica, eluting with ethyl acetate, to give the title compound (30 mg) as a colourless glass.

TLC R<sub>f</sub> 0.27 (EtOAc)

MS 391 (M<sup>+</sup>)

**Example 14**                    **4-((3-(4-Methoxyphenoxy)propylsulfonyl)methyl)-tetrahydropyran-4-carboxylic Acid N-Hydroxy Amide**

To a stirred solution of Example 10 (250 mg) in dichloromethane (15 ml) containing a drop of DMF was added oxalyl chloride (256 mg). The mixture was stirred for 1 h before removing the solvent under reduced pressure. The residue was treated three times with a mixture of dichloromethane/hexane (1:1; 50 ml) and evaporated to dryness. The residue was dissolved in THF (15 ml) and treated with an aqueous solution of hydroxylamine (50 wt%; 0.21 ml). The mixture was stirred for 1 h before diluting with water (10 ml) and extracting with ethyl acetate (3 x 10 ml). The combined ethyl acetate extracts were washed with saturated sodium bicarbonate solution (20 ml), water (20 ml), brine (20 ml), dried over MgSO<sub>4</sub> and evaporated to yield the title compound (145 mg) as a colourless solid.

TLC R<sub>f</sub> 0.60 (9:1 dichloromethane/methanol)

MS 387 (M<sup>+</sup>)

Similarly prepared was:

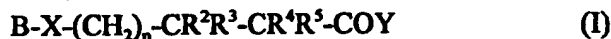
**Example 15**      **4-((3-(4-Phenylphenoxy)propylsulfonyl)methyl)-  
tetrahydropyran-4-carboxylic Acid N-Hydroxy Amide**

From Example 11 (180 mg) as a white solid (124 mg).

- 5    TLC R<sub>f</sub> 0.42 (9:1 dichloromethane/methanol)  
     MS 433 (M<sup>+</sup>)

**CLAIMS**

1. Use of a compound for the manufacture of a medicament for the treatment or prevention of a condition associated with matrix metalloproteinases or that is mediated by TNF  $\alpha$  or enzymes involved in the shedding of *L*-selectin, CD23, the TNF receptors, IL-1  
 5 receptors or IL-6 receptors, wherein the compound is of formula (I)



wherein

- n is 0 or 1;  
 X is S(O)<sub>0-2</sub>;  
 10 Y is OR<sup>1</sup> or NHOH;  
 R<sup>2</sup> and R<sup>4</sup> are independently H or a group (optionally substituted with R<sup>10</sup>) selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, aryl, C<sub>1-6</sub> alkyl-aryl, heteroaryl, C<sub>1-6</sub> alkyl-heteroaryl, heterocycloalkyl, C<sub>1-6</sub> alkyl-heterocycloalkyl, cycloalkyl and C<sub>1-6</sub> alkyl-cycloalkyl;  
 R<sup>1</sup>, R<sup>3</sup> and R<sup>5</sup> are independently H or C<sub>1-6</sub> alkyl;  
 15 provided that not more than two of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are H; or  
 any of CR<sup>2</sup>R<sup>3</sup>, CR<sup>4</sup>R<sup>5</sup> and CR<sup>2</sup>-CR<sup>4</sup> is a cycloalkyl or heterocycloalkyl ring optionally substituted with R<sup>10</sup> or a group (optionally substituted with R<sup>10</sup>) selected from C<sub>1-6</sub> alkyl, aryl, C<sub>1-6</sub> alkyl-aryl, heteroaryl and C<sub>1-6</sub> alkyl-heteroaryl;  
 B is heterocycloalkyl (optionally substituted by R<sup>6</sup> or R<sup>7</sup>) bonded through carbon  
 20 to X, or C<sub>1-6</sub> alkyl-heterocycloalkyl (optionally substituted with R<sup>6</sup> or R<sup>7</sup>), or a group (substituted with R<sup>6</sup>) selected from C<sub>1-8</sub> alkyl, C<sub>2-6</sub> alkenyl and C<sub>2-6</sub> alkynyl;  
 R<sup>6</sup> is N(R<sup>7</sup>)<sub>2</sub>, OR<sup>7</sup>, COR<sup>7</sup>, C(=NOR<sup>7</sup>)R<sup>7</sup>, NR<sup>7</sup>R<sup>8</sup>, S(O)<sub>0-2</sub>R<sup>9</sup> or SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>;  
 R<sup>7</sup> is H or a group selected from C<sub>1-6</sub> alkyl, aryl, C<sub>1-6</sub> alkyl-aryl, heteroaryl, C<sub>1-6</sub> alkyl-heteroaryl, cycloalkyl, C<sub>1-6</sub> alkyl-cycloalkyl, heterocycloalkyl and C<sub>1-6</sub> alkyl-  
 25 heterocycloalkyl, wherein said group is optionally substituted with R<sup>9</sup>, COR<sup>9</sup>, SO<sub>0-2</sub>R<sup>9</sup>, CO<sub>2</sub>R<sup>9</sup>, OR<sup>9</sup>, CONR<sup>1</sup>R<sup>9</sup>, NR<sup>1</sup>R<sup>9</sup>, halogen, CN, SO<sub>2</sub>NR<sup>1</sup>R<sup>9</sup> or NO<sub>2</sub>, and for each case of N(R<sup>7</sup>)<sub>2</sub> the R<sup>7</sup> groups are the same or different, or N(R<sup>7</sup>)<sub>2</sub> is heterocycloalkyl optionally substituted with R<sup>9</sup>, COR<sup>9</sup>, SO<sub>0-2</sub>R<sup>9</sup>, CO<sub>2</sub>R<sup>9</sup>, OR<sup>9</sup>, CONR<sup>1</sup>R<sup>9</sup>, NR<sup>1</sup>R<sup>9</sup>, halogen, CN, SO<sub>2</sub>NR<sup>1</sup>R<sup>9</sup> or NO<sub>2</sub>;  
 30 R<sup>8</sup> is COR<sup>7</sup>, CON(R<sup>7</sup>)<sub>2</sub>, CO<sub>2</sub>R<sup>9</sup> or SO<sub>2</sub>R<sup>9</sup>;  
 R<sup>9</sup> is C<sub>1-6</sub> alkyl, aryl, C<sub>1-6</sub> alkyl-aryl, heteroaryl or C<sub>1-6</sub> alkyl-heteroaryl; and

$R^{10}$  is  $OR^7$ ,  $COR^7$ ,  $CO_2R^1$ ,  $CON(R^7)_2$ ,  $NR^7R^8$ ,  $S(O)_{0-2}R^9$ ,  $SO_2N(R^7)_2$ , CN, halogen or cycloimidyl (optionally substituted with  $R^1$ ); or

a salt, solvate, hydrate, N-oxide or protected amino, protected carboxy or protected hydroxamic acid derivative thereof.

2. Use of claim 1, wherein  $R^2$  or  $R^4$  is optionally substituted  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl-heteroaryl, or  $C_{1-6}$  alkyl-heterocycloalkyl; or  $CR^2R^3$ ,  $CR^4R^5$  or  $CR^2-CR^4$  forms the said optionally substituted ring.
3. Use of claim 1 or claim 2, wherein B is  $C_{1-8}$  alkyl substituted with  $R^6$ .
4. Use of any preceding claim, wherein  $R^6$  is  $OR^7$ .
5. A compound of formula (I) as defined in any preceding claim, with the proviso that Y is not OMe or OEt, when BX is  $HOCH_2CH_2S$ ,  $HOCH_2CH_2CH_2S$  or 2-tetrahydropyranyl-S.
6. A compound of claim 5, wherein X is  $SO_2$ .
7. A compound of claim 5, which is
  - 4-((3-(4-chlorophenoxy)propylsulfanyl)methyl)-tetrahydropyran-4-carboxylic acid or
  - 4-((3-(4-chlorophenoxy)propylsulfonyl)methyl)-tetrahydropyran-4-carboxylic acid or its N-hydroxy amide.
8. A compound of claim 5, which is
  - methyl 4-(3-hydroxypropylsulfanyl)methyltetrahydropyran-4-carboxylate,
  - methyl 4-((3-(4-methoxyphenoxy)propylsulfanyl)methyl)tetrahydropyran-4-carboxylate,
  - methyl 4-((3-(4-phenylphenoxy)propylsulfanyl)methyl)tetrahydropyran-4-carboxylate,
  - methyl 4-((3-(3-pyridyloxy)propylsulfanyl)methyl)tetrahydropyran-4-carboxylate,
  - methyl 4-((3-(4-methoxyphenoxy)propylsulfonyl)methyl)tetrahydropyran-4-carboxylate,
  - methyl 4-((3-(4-phenylphenoxy)propylsulfonyl)methyl)tetrahydropyran-4-carboxylate,
  - methyl 4-((3-(3-pyridyloxy)propylsulfonyl)methyl)tetrahydropyran-4-carboxylate,
  - 4-((3-(4-methoxyphenoxy)propylsulfonyl)methyl)tetrahydropyran-4-carboxylic acid,

4-((3-(4-phenylphenoxy)propylsulfonyl)methyl)tetrahydropyran-4-carboxylic acid,  
4-((3-(3-pyridyloxy)propylsulfonyl)methyl)tetrahydropyran-4-carboxylate,  
4-((3-(4-methoxyphenoxy)propylsulfonyl)methyl)tetrahydropyran-4-carboxylic  
acid N-hydroxy amide, or

5 4-((3-(4-phenylphenoxy)propylsulfonyl)methyl)tetrahydropyran-4-carboxylic acid  
N-hydroxy amide.

9. A compound of any of claims 5 to 8, which is in the form of a single enantiomer  
or diastereomer.

10. A pharmaceutical composition for use in therapy, comprising a compound as  
10 defined in any preceding claim, and a pharmaceutically-acceptable diluent or carrier.

11. Use according to any of claims 1 to 4, wherein the compound is according to any  
of claims 5 to 9.

12. Use according to any of claims 1 to 4 and 11, wherein the condition is selected  
from cancer, inflammation and inflammatory diseases, tissue degeneration, periodontal  
15 disease, ophthalmological disease, dermatological disorders, fever, cardiovascular effects,  
haemorrhage, coagulation and acute phase response, cachexia, anorexia, acute infection,  
HIV infection, shock states, graft versus host reactions, autoimmune disease, reperfusion  
injury, meningitis, migraine and aspirin-independent anti-thrombosis.

13. Use according to any of claims 1 to 4 and 11, wherein the condition is selected  
20 from tumour growth, angiogenesis, tumour invasion and spread, metastases, malignant  
ascites and malignant pleural effusion.

14. Use according to any of claims 1 to 4 and 11, wherein the condition is selected  
from cerebral ischaemia, ischaemic heart disease, rheumatoid arthritis, osteoarthritis,  
osteoporosis, asthma, multiple sclerosis, neurodegeneration, Alzheimer's, atherosclerosis,  
25 stroke, vasculitis, Crohn's disease and ulcerative colitis.

15. Use according to any of claims 1 to 4 and 11, wherein the condition is selected  
from corneal ulceration, retinopathy and surgical wound healing.

16. Use according to any of claims 1 to 4 and 11, wherein the condition is selected  
from psoriasis, atopic dermatitis, chronic ulcers and epidermolysis bullosa.

30 17. Use according to any of claims 1 to 4 and 11, wherein the condition is selected  
from periodontitis and gingivitis.

18. Use according to any of claims 1 to 4 and 11, wherein the condition is selected from rhinitis, allergic conjunctivitis, eczema and anaphylaxis.
19. Use according to any of claims 1 to 4 and 11, wherein the condition is selected from restenosis, congestive heart failure, endometriosis, atherosclerosis and endosclerosis.
- 5 20. Use according to any of claims 1 to 4 and 11, wherein the condition is selected from pelvic inflammatory disease (PID), age-related macular degeneration and cancer-induced bone resorption.
21. Use according to any of claims 1 to 4 and 11, wherein the condition is a lung disease.
- 10 22. Use according to claim 21, wherein the condition is selected from cystic fibrosis adult respiratory distress syndrome (ARDS), emphysema, bronchitis obliterans-organising pneumonia (BOOP), idiopathic pulmonary fibrosis (PIF), diffuse alveolar damage, pulmonary Langerhan's cell granulomatosis, pulmonary lymphangioleiomyomatosis (LAM) and chronic obstructive pulmonary disease (COPD).



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00374

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D309/08 C07D401/12 C07C311/44 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. JANKOWSKI, ET AL.: "Sur les oxathiane-1,4-one-2" BULLETIN DE L'ACADÉMIE POLONAISE DES SCIENCES, SÉRIE DES SCIENCES CHIMIQUES, vol. 19, no. 11-12, 1971, pages 661-672, XP002081718 Warsaw, PL * compound 20 *	5
A	WO 96 35714 A (CHIROSCIENCE) 14 November 1996 cited in the application see page 9 - page 11; claims 1,21	1,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 May 1999

Date of mailing of the international search report

20/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

English, R

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/00374

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9635714 A	14-11-1996	AU 701279 B	21-01-1999
		AU 5698096 A	29-11-1996
		CA 2217857 A	14-11-1996
		EP 0826000 A	04-03-1998